and the populations.

DR. LORBER: Currently, we are approved down to age two. That approval was received fairly recently. We have had some more experience. I can't recall exactly when, but we have been on the market for some time down to age six. I don't, right now, have the numbers offhand as to what the total usage in that pediatric population is relative to adults.

DR. BRASS: But I want to emphasize that, to me, this is really critical that, in terms of the OTC ability, that the postmarketing use becomes a critical safety database and the degree we assume that that database extends equally across the patient populations, that assumption, I think, can't be made unless we see data about those populations.

Similarly, in any of the databases, coming back to the issue about differential handling in the elderly, the issue specifically of somnolence in the elderly taking the standard doses, is anybody aware of any data with loratidine, since it has a dose-related effect on somnolence, whether somnolence in the elderly has been evaluated to a degree that would allow it not to be treated as a

different population in a potential label?

DR. MEYER: I will, again, defer to the company. But I was going to say, I am not aware of any. But I will defer to the company.

DR. LORBER: We haven't done a specific study in geriatric patients to look at the somnolence rates, whether they differ from the younger population.

DR. BRASS: Because, again, as I try to engage in what might be too linear thinking, in the absence of data to the contrary, when we say that there is dose-related somnolence, and that the area under the curve is increased in the elderly, in the absence of data, one might reasonably say that some warning to the elderly, either about increased risk or increased drowsiness specifically might be a potential safety concern unless there was data to the contrary.

Dr. Jenkins?

DR. JENKINS: I just wanted to return to the pediatric issue for a second because I think, as the company pointed out, it is important to note that we have adequate clinical-trial data that convinced the FDA to approve loratidine down to two years of age. As Dr. Meyer pointed out in his

presentation, the adverse experiences that were noted in those clinical-trial databases were really fairly typical of what we have seen in adult patients exposed to loratidine.

There were a few atypical adverse events that showed up a little bit more in children than they did in adults. Those were noted in Dr. Meyer's slide. But the clinical-trial data that we have seen don't really show a variable adverse-event profile versus the use in adults, and loratidine is approved down to age two.

DR. BRASS: Again, my point is simply that we are handicapped by a detailed presentation of that data with denominators, exposures, et cetera, to see how it might or might not confidently extrapolate to widespread OTC use. That is really not in the absolute sense, but to emphasize that, in any further evaluation, the adequacy of the database in an age-appropriate way, needs to be looked at in my opinion.

Dr. Vollmer?

DR. VOLLMER: Following up on the same issue, I have struggled, in looking over these documents, to find in one place a listing of all the various formulations that are now in use and

when they were approved. I have, on page 3 of the Risk Section in the packet, a listing of the approved formulations.

It doesn't list what age groups those go down to, but I was able to infer from elsewhere in the document, at least when they came on board. But then there were references to other formulations that would be considered as well.

Do you have something that we could throw up there so that, as we go through this, we can get very concrete about these are the various formulations about each product and when they came on and which ones, then, as we think about them, we are going to recommend on or not.

DR. MEYER: Let me just say, and I don't want to preclude you folks from giving us input that you feel is helpful, but these questions were framed in a general sense because that is the most crucial advice to us.

As the question was framed, we have data that would have been exhaustive, and details that would have been quite exhaustive, to present to you. But I think what we are more sort of broadly interested in is your overall advice on each compound. We have other information, should your

advice be that we should consider these for OTC marketing.

We can take that advice and factor it in to what we might think of in terms of age range, formulations and so on. Not that we are not happy to receive such advice, but I think that the most critical advice for us is the general question, the molecule.

DR. BRASS: Dr. Barainuk?

DR. BARAINUK: Who regulates the new formulations that would appear if this went OTC; for instance, when Advil-Claritin Cold and Sinus comes out, when these are mixed with herbal remedies which are not FDA regulated--they don't appear to be--who is going to evaluate those and is there the potential for then having toxic effects become apparent?

DR. MEYER: Let me make very clear, because I think this point has gotten a little bit foggy in some of the discussion; we are not here, necessarily, talking about putting these items into a monograph where they can then be sort of mixed and matched under a monograph system with other ingredients for which that is allowed.

So any further formulation, if these were

to be made available in OTC would require a new drug application to support that combination.

DR. BRASS: Dr. Roden?

DR. RODEN: I have sort of quick question. Maybe this is sort of tangential again, but can you give us a sense, you or, perhaps, the sponsor for loratidine, how many prescriptions have been written? It is probably a useful number for us because we sort of have a sense of how many it took, how many terfenadine prescriptions it took, before we got comfortable that we knew the safety profile or lack of in that case?

So, how many prescriptions have there been for loratidine?

DR. BRASS: If you could identify yourself for the transcriptionist, it would be appreciated.

DR. LORBER: Dr. Lorber. I don't have a specific number on hand but, obviously, it is in the millions.

DR. RODEN: Is that 2 millions or 20 millions?

DR. LORBER: Probably tens of millions.

DR. RODEN: I will ask the other sponsors.

DR. BRASS: When we get there. In the absence of further discussion, I am going to call

for a vote on the first question. The vote will be by a show of hands and, please, keep your hands up until I say put them down so that Dr. Titus has a fighting chance of making these add up.

So the question to vote upon is, "Does loratidine have a safety profile acceptable for OTC marketing; i.e., can it be used safely without a learned intermediary?" Let me emphasize, we are going to do both of the following questions. However the vote turns out, we are going to do both the no and yes discussions.

All who believe that the answer to that question is yes, please raise your hand.

[Show of hands.]

MS. TITUS: I am going to have to enter names in the record because there are too many of you. So I am going to ask you to just reach over to the mike and speak your name into the mike for the yesses, please.

DR. BRASS: If we are going to do that, let's just go around the room, starting with Dr. Sachs. Again, a reminder; Dr. Blewitt and Dr. Barainuk don't get to vote.

DR. SACHS: Dr. Sachs; I say no.

MS. CONNER: Brenda Conner; yes.

DR. KRENZELOK: Ed Krenzelok; no.

DR. VOLLMER: Dr. Vollmer; yes.

DR. GILLIAM: Edwin Gilliam; yes.

DR. APTER: Apter; yes.

DR. CANTILENA: Dr. Cantilena; no.

DR. PATTEN: Patten; yes.

DR. WOOD: Wood; yes.

DR. RODEN: Roden; yes.

DR. JOAD: Joad; yes.

DR. KELLY: Kelly,; yes.

DR. JOHNSON: Johnson; yes.

DR. BRASS: Brass; yes.

DR. UDEN: Uden; yes.

DR. FORD: Ford; yes.

DR. D'AGOSTINO: D'Agostino; yes.

DR. DYKEWICZ: Dykewicz; yes.

DR. NEILL: Neill; yes.

DR. FINK: Fink; yes.

DR. WILLIAMS: Williams; yes.

DR. LAM: Lam; yes.

DR. CLAPP: Dr. Clapp; no.

DR. TITUS: So, for the final record, for the counters, I have 20 yesses and 4 nos. But that doesn't add up correctly.

DR. BRASS: Can the no's please just show

their hands again?

[Show of hands.]

DR. BRASS: Dr. Niederman left.

DR. TITUS: Then it is adjusted to 4 no's and 19 yesses.

DR. BRASS: For those who voted no, and anybody else who wants to participate though they would have to explain how, what additional studies should be--what safety or clinical issues should be addressed prior to OTC marketing and what data would be required to change your vote from a no to a yes?

DR. SACHS: I want more safety data, particularly poison control and other things which should be available.

DR. BRASS: So you are suggesting that, at this point, you would not necessarily require additional studies but a more comprehensive review of what is potentially available to make sure there are no signals

DR. SACHS: Yes; and particularly in children which, granted, there is a little more experience, I think, with Claritin and Zyrtec, but, yes.

DR. KRENZELOK: I think the data and

everything really has the appearance of it being relatively safe. I think, in my experience, it would also tell me that all three of them are relatively safe drugs.

However, the problem I have is that I don't think that we have enough evidence to draw that conclusion. I think the data were used rather selectively. With Dr. Sachs, I agree and it is certainly my bias that poison-center data should have been included.

There is a wealth of information out there, over 50,000 antihistamine exposures every year. It is not that expensive in contrast to what the agency said. It is less than $2,000 a year to obtain that data. So, for me to be convinced, I really need to see poison-center data.

DR. BRASS: Dr. Cantilena or Dr. Clapp, anything to add?

DR. CLAPP: As a pediatrician, I have a similar perspective on safety information. I am concerned about a broader spectrum. Also the availability of the drug in the household and the implications it has for children, even if it is not indicated for children.

DR. CANTILENA: Yes; in terms of what I

was thinking is I would like to see this information regarding the QT and the drug-drug interaction either confirmed or handled in terms of the analysis.

When I hear that the correction formula that was used was not appropriate, I would just like to say that when I did the studies with Seldane, I used the same formula. So there is a possibility that there is an effect. I understand that there is a lot of evidence that said there is no problem, and there probably isn't. However, to just ignore this publication, I am not comfortable with.

DR. BRASS: Dr. Blewitt?

DR. BLEWITT: I would just remind the committee that there has been no demonstration that it can be used safely without a learned intermediary.

DR. BARAINUK: I wanted to reinforce that as well, that even though you say that there is no requirement for a use study, I think that it would be absolutely critical to make sure that the people can diagnose themselves appropriately and be treated appropriately.

DR. MEYER: May I follow that up because I

think that if we are going to understand that advice, we need to understand what specifically you would be testing for that is in distinction to the OTC availability antihistamines presently.

DR. BARAINUK: I think that Dr. Ganley opened a can of worms and that is that we would reevaluate how these drugs are used. I think many of the first-generation antihistamines need to be evaluated for their dose-response curves. The decongestants that are used need to be reevaluated for their dose-response curves.

Many of them appear to be overdosed in my patients. Dr. Woosley, at Georgetown, has spent the last three years trying to get a chlorpheniramine study funded federally and can't. Somebody has to pick up the ball and reevaluate how these drugs work given our present knowledge of allergic rhinitis.

DR. MEYER: So, just for clarity's sake, you are not, then, suggesting that these drugs present different issues than antihistamines in general? You are saying that you are of the opinion that all antihistamines should be revisited in their OTC availability?

DR. BARAINUK: I think that, yes, that is

part of the issue. I think the other issue is that these may be a separate class because they don't have the cholinergic side effects so that they won't have the cholinergic benefits that people use them for in the common cold, to go back to that issue.

DR. MEYER: Does that change an allergic-rhinitis patient's ability to detect whether they have the disease or not, the lack of cholinergic properties? Does that make them distinct in terms of the use study that you suggested which was whether patients could correctly diagnose themselves?

DR. BARAINUK: I don't think it would change, necessarily the--yes; it could change the diagnosis because if you have--there are use studies in here comparing first- and second-generation antihistamines. I don't recall which ones it was, but they turned to be equal in efficacy. It is possible that decreasing the mucus discharge, which is due to a parasympathetic cholinergic reflex, with the anticholinergic properties of a first-generation drug, you may find that that is a better answer, though sedating, to one of the second-generation nonsedating

antihistamines.

DR. BRASS: I would like to expand upon the discussion and those who voted yes to comment on the no comments as well as what specific labeling issues you think would be required to meet the standard for your yes vote.

Dr. Wood?

DR. WOOD: I think it would be important that there were some expansion of the label included to highlight to patients the time at which they ought to be looking for advice from a physician. As I read the label right now, that is totally absent. It certainly seems reasonable to me that there is some warning in there that would identify for people, as Dr. Clapp said earlier on--that would tell them when they ought to be seeking further advice from a physician, particularly with children.

DR. BRASS: Dr. Apter?

DR. APTER: I agree with the limitations. Perhaps not at a certain age, over 70, for example, or 65, whatever people consider elderly, if there is no response in one week, if there is fever or other accompanying symptoms, not without a doctor's advice; also, not in renal disease or hepatic

disease without checking with a doctor; not in pregnancy without checking with a doctor; and probably not under the age of 6 without checking with a doctor to be very conservative.

DR. BRASS: Dr. Blewitt, do you have an additional comment that you wanted to make?

DR. BLEWITT: Only, I think, we part ways in terms of first- and second-generation antihistamines, but I do believe that you have to learn under actual use conditions whether people overdose, whether they take these products for the wrong indication such as colds.

There has been no evidence to suggest that we know how the products are going to be used OTC. I think you can explicitly say, "Not used for the common cold."

DR. RODEN: You should add that label to all of the over-the-counter antihistamines except for Tavist; is that correct?

DR. BRASS: It is an interesting philosophical concept, listing the things it is not used for. That is actually a pretty long list. I understand--I am not being completely facetious--that what would be the consumer expectation and whether, for these new products, there be that same

consumer expectation that we require that explicit diverginary warning--

DR. JOAD: I think the reason is that there might be a potential reason why a first-generation might work whereas a second-generation just plain wouldn't work. I guess my other comment, and this is just a wish and I don't think you ever do put them on these product labels, but it would be nice to put something in there that there is a comprehensive management for allergic rhinitis that includes allergen avoidance, check with your physician, something so that they know that the answer doesn't have to be entirely a pharmacologic one.

DR. BRASS: Dr. Vollmer?

DR. VOLLMER: I would concur with most of the previous suggestions about things to add. I feel compelled to state that, while I voted yes, it was under some duress and that I was trying to be compliant with the mandate that you have given us and the conditions under which we are supposed to be providing advice.

So you have made some assumptions which have been challenged throughout the day about should be looking at other things. You said,

"Well, that is not what we are supposed to be talking about today."

I really think that there have been a number of relevant issues raised. Most notably is the actual-use-study issue that you said is off-bounds. So, therefore, trying to focus just on the safety data at hand, I have given a vote but it really makes me feel uncomfortable.

DR. BRASS: Dr. Sachs

DR. SACHS: Even though I voted no, if it is OTC, then there are some warnings which actually don't look like they are addressed here that are coming up for these drugs, in particular maybe not to use or some warning about if you have asthma, if you have a seizure disorder, if you have a heart condition and maybe if you have a bleeding disorder or thrombocytopenia, since these were effects known.

DR. MEYER: I appreciate that advice, but let me restate that, at least for a couple of these drugs, asthma was specifically taken out of the product insert because of safety studies done in asthmatics that showed that they did not make it worse as opposed to the monograph products.

I did want to follow quickly with Dr.

Vollmer, what would your question to take to an actual-use study if one were done?

DR. VOLLMER: I would like to see whether the concerns that have been raised about usage patterns and how they would change, whether people would be getting--whether we would be ultimately increasing or decreasing use of appropriate medicines in the population.

Maybe that is not going to come out of traditionally how a actual-use study is formulated. I don't know. But there are some very fundamental and important issues raised here that have basically been placed off bounds.

DR. BRASS: Dr. Sachs, do you want to finish

DR. SACHS: I'm sorry; not to belabor the point, but yesterday and the day before, I was in the office and I had actually three children who came in who were wheezing who were just identified by their parents as simply having allergies.

So my mentioning and saying something about asthma, that perhaps I should be consulted, is because it does go unrecognized quite a bit.

DR. MEYER: Thank you. I think that can be handled in labeling such saying, "See your

doctor before taking," that sort of thing. So advice appreciated.

DR. BRASS: Dr. Kelly?

DR. KELLY: I would like to second what Dr. Vollmer said. I really have the same concerns. I don't know whether you can formulate a use study to get the information that we need. I am really concerned that all our professional organizations that are involved in the treatment of allergy are not for this.

I think there are some questionable reasons why they may not be for it. On the other hand, there are concerns about undertreatment of the conditions that Dr. Sachs just raised. But the indication is not asthma here. The indication is allergic rhinitis.

I have a little difficulty with the presumption that using antihistamines in the treatment of allergic rhinitis does anything for asthma because there really is not data to support that indication. That is mostly from the use of intranasal corticosteroids.

But the kind of information that I would like to see is use and misuse patterns of OTC versus prescription only. My feeling is that it is

not a whole lot different and that what we are basing this on is pure opinion and not on any data.

DR. BRASS: Dr. Fink?

DR. FINK: I would like to just, I guess, say that I think indications and warnings should be limited to a maximum of five or six because I think we are all aware that as package labeling and package inserts have gotten longer and longer, residents and interns today no longer read them. They go to secondary sources that abstract from them.

I think, for the public, we have got to keep the labeling simple.

DR. BRASS: Dr. Ford?

DR. FORD: I would like to echo some of the sentiments expressed by Bill Vollmer and Dr. Kelly regarding getting more data about the impact. We have heard a lot of about access. I serve a largely indigent population and in answering those questions, I have to speak to the science but, frankly, I am not totally sure about what the impact is going to be.

Certainly, there is a certain level of lack of access that exists right now such that having the drugs OTC may, in fact, increase access.

But if it is still under formularies, chances are that that access might be there in that sense. But I just don't know the answer to that question and we need to know, particularly in certain underserved, vulnerable populations what the impact will have been of such a switch.

DR. BRASS: Dr. Clapp?

DR. CLAPP: I have a concern about the lack of utilization of an actual-use study because the interest that I have in getting information would be on whether or not the actual use would decrease the adequate and appropriate treatment of comorbidities. Whether or not that is interesting, I am not sure the FDA thinks that is the purview of whether or not these drugs should be okayed. It is not because treatment of allergic rhinitis will decrease asthma, but it is that, perhaps, a delay in treatment of allergic rhinitis in an appropriate way, or the misdiagnosis from patients, creates a cascade of events that leads to more complicated medical problems.

So my concern is with this additional medication, these additional medications available, how much are we contributing to the increase of comorbid illnesses. Now, of course, one could say,

well, the same phenomenon could be true with the Benadryl that is over the counter right now. I guess it is kind of ironic to say after you take enough Benadryl you are going to give up quicker, perhaps -- I am not sure -- and perhaps seek medical care a little quicker.

Could you address the issue of comorbidity as an interest in actual-use studies?

DR. GANLEY: I think we are putting some new high hurdles on these actual-use studies as to what you can actually get out of them. As we have gotten into a little more since some of the chronic therapies, such as the cholesterol-lowering or other therapies want to come OTC, we are trying to develop types of protocols to answer these questions and it is very difficult to do.

I get back to one of the reasons why we have depended on the monograph is these same issues that you are raising now apply to the first-generation as well as the second-generation. Again, I point to the fact that this information has been in the docket for a while and none of these issues have been ever brought to the agency.

We are very data-dependent and we can't derive our data ourselves. So it is not just the

burden of Blue Cross and Blue Shield. It is the responsibility of these various professional organizations and other groups to get involved in this if they actually believe that there is a problem out there because we can't really take an action unless we have data to support that action.

If we want to change the monograph, we have to do it through notice and comment. I can tell you that any time we want to go out and change a monograph, we will get challenged by industry if we don't have data to support it, which is justified.

So anyone can provide us with data to support these, but no one is forthcoming.

DR. BRASS: Dr. Neill?

DR. NEILL: The current package insert includes information about hepatic failure or hepatic impairment and renal impairment. I would recommend including some attention to that on an OTC label as well as in patients who are breastfeeding and pregnant.

DR. BRASS: Dr. Johnson?

DR. JOHNSON: I sort of want to reiterate, as several have, that my yes vote was sort of a cautious yes vote. It is really sort of based on

the magnitude of data that we had. In previous meetings, we have had a lot of data to consider and, while the data we saw looked okay, the quantity of the data just wasn't sort of what we were accustomed to so that created sort of a more uncertain yes.

The data we saw, I think I had to answer yes. But it is a little uncomfortable. I do agree with the label recommendations that people have suggested. I think those would be important.

DR. BRASS: Dr. D'Agostino.

DR. D'AGOSTINO: Can I ask a question about the use of the monograph to move this process? I was under the impression that we were appealing to the monograph in terms of our vote here. Is that true, because we are not asking for more data and so forth. We are saying that it is like what the monograph gives its blessing to.

DR. MEYER: No; rather, we are addressing the elements of the Humphrey-Durham Amendment and that is independent of the monograph. It is related, but independent.

DR. D'AGOSTINO: Exactly. And so the fear that some of us have expressed about throwing this into common-cold preparations and so forth is

something we don't have to worry about in terms of the labeling because that is can't happen the way we are giving the yes to this the question?

DR. MEYER: I think that these drugs are now marketed under an NDA. I don't want to talk the specifics of what might happen. I think, though, that we are not talking about a monograph process overtly here.

DR. BRASS: Dr. Gilliam?

DR. GILLIAM: My comment is directed toward the manufacturers in that I would ask that they be a little bit more responsible in their direct-to-consumer advertising. You see adds, Mike Piazza and people running around in the grass and allergens floating all around and that, if they pop a pill, things will automatically get better.

I think they need to do a little bit more of a job of comprehensive management of allergies and asthma.

DR. BRASS: I think we will move on to the second question. Same framework. "Does fexofenadine have a safety profile acceptable for OTC marketing? Can it be used safely without a learned intermediary?" We will begin with Dr. Clapp this time.

DR. CLAPP: No.

DR. LAM: Yes.

DR. WILLIAMS: Yes.

DR. FINK: No.

DR. NEILL: Neill; yes.

DR. DYKEWICZ: Dykewicz; yes.

DR. D'AGOSTINO: D'Agostino; yes.

DR. FORD: Ford; yes.

DR. UDEN: Uden; yes.

DR. BRASS: Brass; yes.

DR. JOHNSON: Johnson; yes.

DR. KELLY: Kelly; yes.

DR. JOAD: Joad; yes.

DR. RODEN: Roden; yes.

DR. WOOD: Wood; yes.

DR. PATTEN: Patten; yes.

DR. CANTILENA: Cantilena; yes.

DR. APTER: Apter; yes.

DR. GILLIAM: Gilliam; yes.

DR. KRENZELOK: Krenzelok; no. And Vollmer asked me to vote no for him as well. He had to step out.

DR. BRASS: Doesn't count.

DR. KRENZELOK: Okay; I tried.

MS. CONNER: Conner; yes

DR. SACHS: Sachs; no.

DR. BARAINUK: Barainuk. I'm sorry, Mr. Chairman, I refuse to answer that question because I might intimidate myself.

DR. TITUS: We have 18 yesses and 4 nos.

DR. BRASS: And one abstention.

DR. VOLLMER: No.

DR. BRASS: Dr. Vollmer was a no.

DR. TITUS: So I am going to correct the vote to 18/5.

DR. BRASS: Same discussion but we don't need to repeat everything we just said. So, for the no's, are there issues that did not come out earlier that are fexofenadine-specific that you would like to point out?

Dr. Fink?

DR. FINK: My primary reason for changing my vote on this product is, as a pediatrician, I don't think the data on fexofenadine in pediatrics with the changing dosing formulations is really adequately developed for over-the-counter labeling yet.

DR. BRASS: But would a label that said twelve or over have yielded a yes vote?

DR. FINK: Absolutely.

DR. BRASS: So, we won't change anything, but you should have voted yes.

DR. BRASS: Dr. Vollmer?

DR. VOLLMER: My vote was specifically related to an issue that was raised in the FDA analysis regarding a possible risk to seizures which is specifically not listed in the product label. If that was there, I would be content to vote yes.

DR. BRASS: Yes?

DR. KRENZELOK: I will just reiterate my last points and say we don't have enough evidence, I don't think, really to draw any conclusions.

DR. BRASS: Are there label-specific issues for fexofenadine for the yes votes that people feel are important. I will emphasize the apparent, much weaker, pediatric database under the theme that we were talking about earlier.

DR. APTER: I would leave off the 180-milligram dose.

DR. BRASS: Because?

DR. APTER: It has only been on the market a year.

DR. BRASS: The logic being that there is less of a safety database to support the higher

dose?

DR. APTER: Right.

DR. BRASS: I would mention, again, if there is a potential for food or antacids or whatever the mechanism of the antacid is to lower the AUC by half, I would be concerned about loss of efficacy and some kind of statement, "Do not take with." Again, I think the comments about, "If symptoms do not improve within a week," and fever and all those other comments that were made, I think will apply to all three so we don't need to reiterate those each time.

But I think the theme of that helped the consumer was important.

Yes?

DR. JOAD: Can I just comment about if the symptoms don't improve within a week -- a season is more than a week, so if it is for seasonal allergic rhinitis, you wouldn't put in, "If it doesn't get better, go see your doctor." "If it doesn't improve within your season," or, "If it doesn't work."

DR. BRASS: My point is if that the patient hasn't gotten symptomatic relief in a week--

DR. JOAD? Within a week; okay.

DR. BRASS: You would like them to go see their physician as a cue that additional intervention may be required.

DR. JOAD: Okay. "If it doesn't work, go see your physician." But they don't have to. They are not limited to one week.

DR. BRASS: I understand, but some time frame of expectation for the consumer is helpful to know when to judge lack of efficacy.

DR. JOAD: Lack of efficacy. But, if it is working, they would take it for the season; right.

DR. BRASS: Other comments, questions?

Moving on to the third question, then. "Does cetirizine have a safety profile acceptable for OTC marketing; i.e., can it be used safely without a learned intermediary?" Beginning with Dr. Johnson and moving around the room that way.

Point of order?

DR. FINK: Just a question. With this drug, I think there are some issues that may engender some discussion before a vote because I do see this drug as having significantly different issues than the previous two.

DR. BRASS: Okay. Fine. Would you like to begin that discussion, then?

DR. FINK: I think the question of how much sedation is acceptable is potentially a real issue.

DR. BRASS: When you say "how much," how much to get away without a warning or how much is safe? Let me remind--I think I am correct is that the existing prescription label indicates somnolence for this product in difference to the other two and that somnolence associated to the degree with the first-generation has been deemed not to be a safety concern that blocks OTC use.

Does that help?

DR. NEILL: Earlier you brought up thrombocytopenia. As a byproduct of hydroxyzine, I would be interested in specific examples from the hydroxyzine data about whether or not that has appeared as a sentinel event, an indicator, and, if so, what is the data or did the FDA review that specifically but just not separate it out?

DR. MEYER: We did not review it separately. We did not specifically review the experience with hydroxyzine because this is a metabolite of hydroxyzine but it is not necessarily

the only one.

I would, since I have the mike and we are talking about thrombocytopenia, convey the answer to a question earlier about any positive rechallenges. We have no positive rechallenges known, or known positive rechallenges.

DR. BRASS: Thank you.

DR. CANTILENA: Just a question. Am I to understand that the current drug label for Zyrtec has a statement in there about the QT interval? Is that true and is that in contrast to the others?

DR. MEYER: The clinical pharmacology section--I believe it is in the clinical pharmacology section--does review or refer to the four studies that we done for cardiac safety and does refer to--this was actually in the setting of the ketoconozole drug-interaction study which there isn't really much of a drug interaction between the two.

But, in fact, there was an effect with Bazett's correction seen with ketoconozole. There was one seen in that one study with cetirizine. And there was an additive effect in the patients given both together, again using Bazett's correction.

That is in contradistinction to the other data and that is basically what the label says, that there are these four studies only one of which showed this. But that is true. We don't have that sort of study from the NDA database with the other products.

DR. CANTILENA: Okay. In that regard, then, each--so there was a small effect on the QT in one of four studies. There was an effect there from the antihistamine alone and an additive with the effect of ketokonozole? Is that true?

DR. MEYER: Right. Just ballpark numbers. They were both in the range, the single agents, the ketoconozole and the cetirizine, were both in the range of 8 to 9 and the additive effect was about 17 milliseconds using Bazett's correction.

DR. CANTILENA: How about change in heart rate because, you know, you talk about the correction formula.

DR. MEYER: I don't know the specifics of the data from that study but, in general, I believe there is a change, a somewhat small change, in heart rate with cetirizine. But I don't know the specifics from that study offhand.

DR. CANTILENA: So the heart rate goes up

on antihistamine? Okay. So, then, I guess you are comfortable with sort of dropping that information from an OTC label because it would be hard to know if the consumer would understand that.

DR. MEYER: I think if we were concerned that there was a real QT effect with cetirizine, and it occurred in the setting of drug-drug interaction, from our prior history, we would not only be concerned about that being marketed OTC, we would be concerned about it being marketed at all.

DR. BRASS: Dr. Barainuk?

DR. BARAINUK: Going back to the drowsiness issue, clinical practice is generally to give the drug at night. I don't know if that can be a recommendation on the package insert or not, but it is a way to get around the problem since it does last for 24 hours.

DR. BRASS: Are the data to support the time course of the drowsiness--do you think in addition to a drowsiness warning or instead of a drowsiness warning?

DR. BARAINUK: It is general practice for us to prescribe it at night because of the proportion of people who do get drowsy so that they won't have the risks of driving or operating heavy

equipment.

DR. BRASS: Again, my question is is it clear that by 8:00 a.m. the next morning, there is no significant drowsiness if you take it at 10:00 p.m. at night?

DR. BARAINUK: That has been my clinical experience. I don't think that that actually has been--I don't believe there is published data that the next morning that you are still drowsy.

DR. BRASS: Does anybody know what the time-to-peak of cetirizine is? Does the FDA have that data, the pharmacokinetics, what is the time to peak cetirizine concentration after a single dose?

DR. MEYER: It may be in the label. I don't have the label open in front of me right now.

DR. BRASS: Dr. Wood?

DR. WOOD: This is to Bob Meyer. Would it be fair to say that your comfort level with cetirizine is less than with the others in terms of the side-effect profile? That is, perhaps, an unfair question.

DR. MEYER: I am not sure that is a fair characterization. I think it is somewhat different. I think there is an acknowledgment from

the data that the propensity for it to cause CNS effects including sedation is somewhat different from the other two drugs that we are talking about today.

I don't think we have data to suggest that it is different in terms of absolute from the OTC drugs and it looks like it is probably better in many of these features than the OTC drugs. But we don't have specific data head-to-head--we don't--to make definitive statements in that regard.

DR. WOOD: In the thrombocytopenia?

DR. MEYER: I really think, looking at the thrombocytopenia, that some of that is being driven by reports such as Internet reports and so on. So it gets kind of kicked up there and I think we needed to pay attention to it because it stands out in the list of top tens.

But if you actually look down in the data, I don't think it is a signal that is any stand-out either in comparison to the other drugs or in general.

DR. WOOD: If I understood your response already to the hepatic failure issue, you did not think that was significant; is that fair?

DR. MEYER: I think, on balance, we can't

definitively say that it is not an issue but that would also be an approvability issue overall and not just an OTC market issue. As I said, nothing we have found at this point has led us to believe that there are any approvability issues with these three agents.

DR. BRASS: Dr. Neill?

DR. NEILL: You mentioned earlier that there is no rechallenge data in the cetirizine but there is one death. I am reminded of the discussion of PPA at our last meeting where data regarding people who died could not be collected because they were dead.

I can't imagine that that would not have skewed our discussion of this. I understand that they, in fact, were rechallenged and that that case has been reviewed. I take you at face value that that seems not to have been causally related to cetirizine, but there was a death.

DR. BRASS: Dr. Sachs

DR. SACHS: Well, the thought with thrombocytopenia, I was just curious if anyone had spoken with the hematology people or oncology colleagues or if anyone here happens to be hematology/oncology who could comment.

DR. MEYER: Can we make a comment on the death case. While my colleague from OPMRA is coming up, I did want to state that the T-max for cetirizine, at least as far as pharmacokinetics, is one hour. What the effect is for sedation in terms of the maximal effect or the timing of that, I don't know.

DR. TRONTELL: In the review of the thrombocytopenia cases, we used a very liberal inclusion criteria and the death occurred in a thirteen-year-old who had already had two liver transplants, bile-duct stenosis, irritable-bowel syndrome, multiple allergies, was also on tacrolimus and had developed thrombocytopenia, suffered an intracranial hemorrhage and died. So the case is actually quite complex when you look at other factors that may have contributed to the patient's illness.

DR. BRASS: Dr.Fink?

DR. FINK: I think one of the reasons I am feeling a little bit uncomfortable about this drug in trying to think to think about it is the fact that the sponsor of the drug is not here today for questioning and we haven't had an opportunity to ask them about any data they have in comparison to

the other two drugs seems to put us at some disadvantage in judging whether they have any data that should affect our decision.

DR. BRASS: Dr. Vollmer?

DR. VOLLMER: Yes. It was noted that cetirizine is the active metabolite of hydroxyzine. Being a naive statistician who is not a physician here, I assume that is one of the first-generation antihistamines? Is that correct?

DR. MEYER: Hydroxyzine is an antihistamine that does not--it is not available over the counter. It is generally used for things like pruritus and anxiety, actually. Atarax or Vistaril are the trade names for those. I do want to stress that this is a metabolite of hydroxyzine, unlike, say, the terfenadine-fexofenadine case.

DR. VOLLMER: So this is a very different situation to that?

DR. MEYER: It is a different situation from that.

DR. BRASS: If there are no other comments or questions, I will, again, read the third question. "Does cetirizine have a safety profile acceptable for OTC marketing; i.e., can it be used safely without a learned intermediary?"

Dr. Johnson?

DR. JOHNSON: Yes.

DR. BRASS: Dr. Kelly?

DR. KELLY: Yes.

DR. JOAD: Joad; yes.

DR. RODEN: Roden; Yes.

DR. WOOD: Wood; yes.

DR. PATTEN: Patten; yes.

DR. CANTILENA: Cantilena; yes.

DR. APTER: Apter; yes.

DR. GILLIAM: Gilliam; yes.

DR. VOLLMER: Vollmer; no.

DR. KRENZELOK: Krenzelok; no.

MS. CONNER: Conner; yes

DR. SACHS: Sachs; no.

DR. CLAPP: Clapp; no.

DR. LAM: Lam; yes.

DR. WILLIAMS: Williams; yes.

DR. FINK: Fink; yes.

DR. NEILL: Neill; yes.

DR. DYKEWICZ: Dykewicz; yes.

DR. D'AGOSTINO: D'Agostino; yes.

DR. FORD: Ford; yes.

DR. UDEN: Uden; yes

DR. BRASS: Brass; yes.

DR. TITUS: There are 19 yesses and 4 nos.

DR. BRASS: Do those who vote no have any additional comments to make other than those we made in the context of the other two products?

Don't leave. There's lots of good things going to happen yet.

Yes; Dr. Vollmer?

DR. VOLLMER: I would just say that, for me, there really is qualitatively a lot less data, it seems, on this product than on the other two. That is my main reservation. Because of the link with Allegra in the previous formulation, and the longer history with that, the fact that Claritin has been around for the longest time in the U.S. and also its OTC use elsewhere, from my own point, we had a much longer history and I just felt that this is--I just need more time.

There is nothing in particular that alarmed me but I just would like to see more time with this drug.

DR. BRASS: In the yes votes, are there specific warnings, and let me just begin. I think this is a case where there would need to be a drowsiness warning and the same type of driving warnings associated with the first generation. I

think liver disease, renal disease in the elderly are all potential additional complicating factors which, in the absence of data, would need special warning based on just the pharmacokinetics and dose-relatedness of the somnolence.

Are there other points that people would like to make?

PANEL MEMBER: Would bruising be an additional one?

DR. BRASS: What would you propose it would actually say?

PANEL MEMBER: Discontinue if you discover bruising or something to that--no? Or you could preempt it, "If you have a bleeding disorder, do not take."

DR. BRASS: I think the latter. I am not sure if there is data to support any of those. I am sure the FDA has standard consumer-oriented language for drugs that have a risk of thrombocytopenia. But I am unconvinced whether the signal is clear. Even though I was very concerned about it, I am unconvinced whether the signal requires special consideration of thrombocytopenia as a risk.

DR. WOOD: If the drug has a risk of

thrombocytopenia, it shouldn't be on the market, period. We shouldn't be warning people not to take it if they might bleed. If we really think that is true, it should be removed from the market.

DR. BRASS: Not an OTC issue. It market issue.

DR. WOOD: Right.

Does the FDA have sufficient clarification of these issues from the committee consistent with its objectives?

DR. MEYER: I believe we do. I would like to thank the committees for their very well-thought-out discussion today and their advice and we appreciate you being here and giving us your expertise. Thank you.

DR. BRASS: I am also going to request 60 minutes of personal-privilege time--60 seconds; I'm sorry. This is my last meeting as Chair of this committee and I would just like take this opportunity to thank Dr. Titus for all her efforts as Executive Secretary of this committee, the FDA for putting together consistently interesting meetings, all my colleagues on the NDAC Panel, other panels, and all the sponsors who have cooperated.

Particularly today, I would like to, again, thank all the committee members dealing with some very challenging issues, trying to keep focused to address the agency needs, and the cooperation of the petitioner and sponsor in helping us address those.

The meeting is now adjourned.

[Whereupon, at 4:23 p.m., the meeting was adjourned.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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